Towards defining the threshold between low and high glucose variability in diabetes mellitus

Louis Monnier [1], MD, Claude Colette [1], PhD, Anne Wojtusciszyn [2], MD, Sylvie Dejager [3], MD, Eric Renard [2], MD, Nicolas Molinari [4], PhD, David R Owens[5], MD

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Affiliations of the authors

1 Institute of Clinical Research, University of Montpellier, Montpellier (France)
2 Department of Endocrinology, Diabetes, Nutrition, Montpellier University Hospital, University of Montpellier, Montpellier (France)
3 Department of Endocrinology, Hospital Pitié Salpétrière, Paris (France)
4 UMR 5149, Department of Statistics and Epidemiology, Montpellier Hospital, University of Montpellier (France)
5 Diabetes Research Group, Swansea University, Wales (United Kingdom)

Corresponding author
Professor Louis Monnier, University of Montpellier, Institute of Clinical Research, 641 Avenue du doyen Giraud, 34093 Montpellier Cedex 5 (France)
Tél: +33 411 759 891
e-mail: louis.monnier@inserm.fr

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Abbreviations used throughout the text:
GV: glucose variability
%CV: Percentage Coefficient of Variation for glucose

ABSTRACT

Objective

To define the threshold for excess glucose variability (GV), one of the main feature of dysglycemia in diabetes.

Research design and methods

A total of 376 persons with diabetes investigated at the University Hospital of Montpellier, France, underwent continuous glucose monitoring. Participants with type 2 diabetes were divided into several groups: Groups 1, 2a, 2b and 3 (n=82, 28, 65 and 79, respectively) according to treatment (1) diet and/or insulin sensitizers alone, (2) oral therapy including an insulinotropic agent, DPP-4 inhibitors (group 2a) or sulfonylureas (group 2b) or (3) insulin. Group 4 included 122 with type 1 diabetes. Percentage Coefficient of Variation for glucose (%CV=[(SD of glucose)/(mean glucose)] x100) and frequencies of hypoglycemia (interstitial glucose < 56 mg/dL, 3.1 mmol/L) were computed.

Results

Percentages CVs (median [IQR],%) increased significantly ($p<0.0001$) from group 1 (18.1 [15.2-23.9]) to group 4 (37.2 [31.0-42.3]). In group 1, the upper limit of %CV, which served as reference for defining excess of GV, was 36%. Percentages of patients with %CVs above this threshold in groups 2a, 2b, 3 and 4, were 0, 12.3, 19.0 and 55.7%, respectively. Hypoglycemia were more frequent in group 2b ($p < 0.01$) and groups 3 and 4 ($p < 0.0001$) when subjects with a %CV> 36% were compared to those with %CV≤ 36%.

Conclusions

A %CV of 36% appears to be a suitable threshold to distinguish between stable and unstable glycemia in diabetes since beyond this limit the frequency of hypoglycemia is significantly increased especially in insulin-treated subjects.

At present, there is incontrovertible evidence that chronic hyperglycemia is a key player in the pathogenesis of all related-diabetes complications, both in type 1 [1,2] and type 2 diabetes [3,4]. However glucose variability (GV) and hypoglycemia, the second and third components of the "glucose triumvirate" [5] may also be considered as risk factors for vascular complications in diabetes mellitus. Excess GV is usually associated with increased risk of hypoglycemic events necessitating a global therapeutic approach aimed at avoiding hypoglycemic episodes whilst maintaining the HbA1c levels within an individually defined target range according to patient-centered therapeutic strategies [6]. HbA1c-based strategies are limited by the fact that they do not integrate the GV and at present the role of GV on the development and progression of cardiovascular diseases remains a subject of controversy [7-9]. The proof-of-concept FLAT-SUGAR randomized interventional study [10], was designed to identify a difference in GV between two groups of insulin-treated subjects with type 2 diabetes. These participants were assigned either to continue basal-bolus insulin after a run-in period or to replace the premeal short-acting insulin analog with mealtime dosing of exenatide while continuing the basal insulin glargine. The secondary outcome of the FLAT SUGAR trial was to test the hypothesis that improvements in GV in insulin-requiring diabetes can exert beneficial effects on markers of cardiovascular risk. As hypoglycemic episodes and GV, concomitantly or separately, are potential causative factors for cardiovascular events, the question arises as how to separate the patients with unstable diabetes from those considered stable. Therefore, we should identify a threshold for the amplitude of GV below which the risk of hypoglycemia would be negligible. Consequently we analyzed continuous glucose profiles from groups of patients with type 1 or type 2 diabetes to gain further insight into this conundrum. Data from those subjects treated only with diet alone or with the addition of insulin sensitizers, which represent little or no risk of hypoglycemia (reference group), were used to determine the upper level of GV to define the threshold between stable and unstable diabetes. Patients from the other groups were compared to the reference group to determine the proportion of exaggerated glycemic fluctuations and frequency of accompanying hypoglycemic episodes. This aspect is crucial when it comes to healthcare providers in order to achieve and sustain optimal glycemic control by achieving and maintaining GV within a reasonable range and with minimal risk of hypoglycemia. Presently there are clear recommendations for the management of chronic hyperglycemia with most organizations

recommending a target HbA1c level of 7% (53 mmol/mol) [6,11]. However, to date there are no recommendations provided for GV, which this present study is designed to address.

RESEARCH DESIGN AND METHODS

Study design and participants

A total of 376 persons with either type 1or type 2 diabetes were included in the study between 2003 and 2012. All participants regularly attended the outpatient clinic of the University Hospital of Montpellier (France) and were entered consecutively without any selection based on HbA1c, age, sex, duration of diabetes or diabetic complications. The study was observational in design and the data were retrospectively analyzed. Out of the 376 patients included in this study, 82 type 2 diabetes were treated with diet and/or insulin sensitizers alone. These patients, referred to as group 1, were selected to serve as reference for stable glucose homeostasis diabetes. The rationale for this choice was based on two main principles and observations. Firstly, patients treated with insulin sensitizers alone correspond usually to persons who are at an early stage in the natural history of type 2 diabetes. Such patients have usually relatively small glucose fluctuations that are mainly due to postprandial excursions and which remain relatively constant across the HbA1c spectrum [12]. Secondly, this group corresponds to patients in whom the risk of hypoglycemic episodes is also very low or even absent [13] and who, consequently, have a low likelihood that glycemic variability be compounded by glycemic rebounds due to correction of symptomatic hypoglycemia. Type 2 diabetic patients treated with oral hypoglycemic agents known to have insulinotropic effects were excluded from the reference group even though DPP-4 inhibitors stimulate the endogenous insulin secretion in a glucose-dependent manner [14], which theoretically excludes the risk for hypoglycemic events.

Besides the reference group, other groups of patients were selected by types of diabetes and categories of antidiabetic treatments. Their detailed characteristics are reported later at the beginning of the results section.

Considered as a whole, all patients were stable on their respective treatment regimens for at least three months prior to the investigations. The 376 patients included in the present study were selected among a total population of 559 subjects with type 1 or type 2 diabetes who underwent 3-day ambulatory continuous glucose monitoring (CGM). Criteria of exclusion from the initial screened list of potential participants included those who had experienced a recent illness or been treated with steroids during the 3-month period preceding the

investigation. In addition, exclusion criteria from the final analysis were unexpected disruptions in the glucose monitoring or insufficient number of capillary tests on whole blood glucose for the calibration of the CGM (four tests were required daily for this purpose). Acceptable calibration meant an accuracy criterion with a correlation coefficient > 0.79. All the investigations were routinely performed in the diabetic outpatient clinic of the University Hospital of Montpellier (France) and were in accordance with the Helsinki Declaration [15]. As the study was observational in design, each participant gave an oral informed consent in accordance with European directives that require no approval from an ethics committee due to the non-interventional design of the study [16].

Clinical investigations and laboratory determinations

All participants underwent ambulatory continuous glucose monitoring (CGM) for 3 consecutive working days, avoiding the weekend, using the same technology during 2003 to 2012 (i.e. second-generation MiniMed system [Medtronic, Northridge, CA]). The sensor was inserted on day 0 (before 1200 h) and removed on day 3 at the same time point as on day 0. Chronic hyperglycemia was assessed on study day 0 based on HbA1c levels, determined using a high-performance liquid chromatography assay [17] (Menarini Diagnostics, Florence, Italy).

Analysis of the data from the CGM

CGM was used to calculate the mean 24-h glucose concentration and SD (standard deviation around the mean glucose value). GV was determined using the percentage Coefficient of Variation for glucose (%CV) obtained from the following computation: [(SD of glucose)/(mean glucose)] x 100. The percentage Coefficient of Variation for glucose is probably one of the most reliable markers to assess the amplitude of GV as it is adjusted for the mean glucose value and does not depend on this parameter [18,19,20]. Furthermore, it is well known that all parameters described for assessment of GV are highly intercorrelated [21-23] and some investigators have established that the %CV is a valid GV index especially when used in combination with other more complex metrics of glycemic control [22]. It should also be appreciated that healthcare professionals by reading simple metrics such as the mean 24-h glucose value and the SD provided by CGM systems and printed on the files associated with traces of the glycemic profiles can easily calculate the %CV. For the aforementioned reasons and as the aim of our study is essentially pragmatic in its objectives, we have deliberately not studied the more sophisticated indices of GV such as the MAGE

(Mean Amplitude of Glycemic Excursions), the MODD (Mean Of Daily Differences), the CONGA (Continuous Overlapping Net Glycemic Action), the LBGI (Low Blood Glucose Index) and others [24-26]. Many of these indices have been widely described and more commonly used in type 1 diabetes and not type 2 diabetes [23]. In addition, some of these metrics such as the LBGI for hypoglycemia [27] are more oriented towards the risk analysis of adverse events relevant to GV than towards the specific assessment of GV.

Based on two validated 24-h glycemic profiles on study days 1 and 2, the SDs, 24-h mean glucose values and %CVs were averaged for these two consecutive days. The data recorded on day 0 were excluded from the analysis in order to avoid any bias due to glucose stabilization between the sensor and the interstitial fluid during the first hours after insertion of the device. Calculations were made at 5 minute-time intervals. In each group, the relative frequency for distributions of %CV values was tested for normality using the Shapiro and Wilk test [28]. However, as this test failed to demonstrate a unimodal, non-skewed Gaussian distribution, the analyses were performed using non-parametric statistics: medians and interquartile ranges. As mentioned above, group 1 patients were taken as reference for 'stable' diabetes, in view of the small/absent risk of hypoglycemia and limited glucose fluctuations. The upper limit of %CVs in group 1 ($\%CV_{max1}$) was referred to as the threshold between stable and unstable glycemic control. In all groups, including group 1, the presence of hypoglycemia based on the 24-h glucose profile was considered as a whole. When applicable, i.e. when some individuals of a given group had %CV greater than the $\%CV_{max1}$, the patients of this group were tested for the presence of hypoglycemia after they had been divided into 2 subgroups according to whether %CVs were above or below the $\%CV_{max1}$ determined in the reference group. Hypoglycemia was defined as 3 consecutive interstitial glucose levels < 56 mg/dL (3.1 mmol/L) with time spent ≥ 15min. Hypoglycemic episodes were reported by reading the 24-h glucose profiles.

Additional calculations and statistical analysis

Except for hypoglycemia, comparisons between groups or subgroups were made using the non-parametric Kruskall-Wallis or the Mann and Whitney tests as appropriate. In groups 2a, 2b, 3 and 4, percentages of %CVs above the $\%CV_{max1}$ were calculated. Comparisons between percentages in the different groups were made using the Chi square or exact Fisher test. The number of hypoglycemic episodes expressed as number per patient-day was compared between groups and between subgroups exhibiting stable ($\%CV \leq \%CV_{max1}$) and unstable

(%CV > $\%CV_{max1}$) glucose homeostasis. For that purpose, Poisson regression models were fitted after plotting the number of hypoglycemic episodes as dependent variable and groups of patients as explanatory variable. Simple correlations between either SD or %CV and mean glucose values were calculated using the Spearman rank test. All p values were considered significant when < 0.05. Data were analyzed using the R software version 3.2.3.

RESULTS

Of the 376 persons who were included in the present study, 122 had type 1 diabetes and 254 type 2 diabetes, which were further divided into several groups. Among those with type 2 diabetes, 82 (group 1) were on either dietary measures alone (n = 8) or on treatment combining diet with insulin sensitizers (metformin and/or glitazones, n = 74), 93 (group 2) received dual or triple oral antidiabetic therapy combining one or two insulin sensitizers with at least one insulinotropic agent, either a DPP-4 inhibitor (sitagliptin or vildagliptin, subgroup 2a, n = 28) or a sulfonylurea (glimepiride or glibenclamide, subgroup 2b, n = 65). Finally 79 (group 3) were on insulin treatment prescribed as either basal insulin alone (n = 33) or basal-bolus insulin regimens (n = 46). The 122 subjects with type 1 diabetes (group 4) were treated with either basal-bolus regimens delivered as multiple injections (n = 97) or by subcutaneous insulin pumps (n = 25). Demographic characteristics of patients, treatment categories and laboratory data in the different groups are shown in table 1.

Comparison of parameters of glycemic control in the different groups

The median HbA1c levels were significantly lower (p<0.0001) in orally treated groups (1, 2a and 2b) than in the insulin-treated groups (3 and 4).The SDs (median [IQR], mg/dL) steadily and significantly (p<0.0001) increased from group 1 (25 [19-33]) and group 2a (23 [19-28]) to group 4 (58 [44-73]). Similar results were observed for %CVs (median [IQR],%) that increased from 18.1 [15.2-23.9] in group 1 and 18.6 [16.6-22.4] in group 2a to 37.2 [31.0-42.3] in group 4 (p<0.0001). Furthermore in group 3 the %CVs (median [IQR]) were approximately the same in patients on basal insulin (29.7 [23.1-35.1], n = 33) as in those on basal-bolus insulin regimen (26.9 [19.5-34.3], n = 46).

Distributions of percentage Coefficients of Variation for glucose (%CV) in the different groups

Histograms of relative frequency distributions for %CVs are given in figure 1. In the reference group (group 1), the upper limit of the distribution of %CV was found to be of 36%,

which was adopted as reference threshold ($\%CV_{max1}$) to separate stable from unstable glycemia. In the particular setting of our population, percentages of patients exhibiting %CVs above this upper limit were found to be of 0%, 12.3%, 19.0% and 55.7% in groups 2a, 2b, 3 and 4, respectively. Differences between percentages were statistically significant ($p < 0.0001$) when group 4 was compared to groups 2a, 2b and 3. Furthermore by pooling all subjects with type 2 diabetes without any hypoglycemia (n = 154), the upper limit of distribution of %CV was 38%, i.e. a value quite similar to that observed in the reference group (36%).

Number of hypoglycemic episodes in the different groups

The results are represented in figures 2 and 3. Groups 1 (reference group) and 2a patients (DPP-4 inhibitor + insulin sensitizers) were almost devoid of hypoglycemia. Hypoglycemia occurred in all the other groups and were more prevalent in type 1 diabetic patients ($p < 0.0001$, group 4 vs groups 1, 2a, 2b and 3) (figure 2). As illustrated in figure 3, the frequency of hypoglycemia was significantly greater in the subgroups with a %CV > 36% than in the subgroups with values ≤ 36% ($p< 0.01$ in group 2b; $p< 0.0001$ in groups 3 and 4). Medians of 24-h mean glucose values between subgroups with a %CV> or ≤ 36% were slightly different in group 3 ($p=0.018$) but not in groups 2b and 4 (figure 3).

Relationships between parameters of glucose variability and 24-h mean glucose concentrations

In the study population considered as a whole (n = 376), SD correlated positively and significantly with 24-h mean glucose concentration ($rhô = 0.50$, $p < 0.0001$) while the %CV did not ($rhô = 0.04$, $p = 0.42$).

CONCLUSIONS

There are two main messages emanating from the present study. Firstly, GV represented by the %CV was greater in the subjects with type 1 than in type 2 diabetes and there was a steadily increasing glucose variability across the continuum of type 2 diabetes from those on diet with or without insulin sensitizers and those treated with DPP-4 inhibitors to those receiving sulfonylureas and finally those subjects on different insulin regimens. Secondly, a threshold for %CV of 36% permits discrimination between those with stable or unstable glucose homeostasis. However, one of the remaining questions is to know whether GV should be assessed in diabetes care as we are still awaiting the findings from interventional studies

designed to evaluate whether lowering GV to within near normal limits can prevent the development and/or progression of diabetic complications. However, the recent publication of the results of the FLAT-SUGAR Trial [29] does not provide any compelling evidence that reduction of GV can result in improvements of certain cardiovascular bio-markers such as CRP, interleukin 6 or urinary prostaglandin F2α, representing the inflammatory or oxidative stress status [30].

Nevertheless, even though the relationship between GV per se and adverse cardiovascular outcomes has not been established, it remains that increased glucose fluctuations can play a consistent role in precipitating hypoglycemia [26,31]. Highly significant correlations have been observed in persons with diabetes treated with insulin between the percentage coefficients of glucose variation (%CV) and risk of hypoglycemia [20,22]. Fabris et al reported a correlation coefficient as high as 0.81 between the %CV and percentage of values below a glucose target set at 70-180 mg/dL (supplementary data) [22]. In the present study, we similarly found a relationship between the %CV and frequency of hypoglycemia, which was significantly greater in subjects who had a value above 36% than in those who were below this threshold. It should be noted that this evaluation was mainly conducted to validate our primary objective, i.e. the determination of the threshold between low and high glucose variability in persons with diabetes mellitus in the particular setting of our study. Bringing all these observations together, healthcare professionals should be encouraged to achieve a lowering of GV especially when patients are affected by exaggerated glucose oscillations. Such an approach requires the definition of an upper limit of GV in order that clear instructions can be provided to both patients and healthcare providers. Therefore, indices recommended for the GV assessment must be easily accessible and computable by any healthcare professional. Consequently, determining the %CV appears to be more suitable than the other more complex indices mentioned above [18,19,24]. According to our results, obtained by analyzing the frequency distribution of GV in the reference group, a threshold for %CV of approximately 36% seems appropriate for this purpose. A few years ago, basing his statement on personal observations Hirsch proposed as ideal target for glycemic variability a SD calculated from the following formula: SD x 3<Mean Glucose, i.e. a %CV < 33% [32]. More recently, Rodbard [19] found that by stratifying insulin-treated patients (both type 1 and 2 diabetes) according to whether the %CV corresponded to the 25th, 50th, and 75th percentiles of the data distribution, a cut-off value between high (fair and poor) and low (good and excellent) of 36% can be set. This threshold

is exactly the same as that observed in our study. However, one of the strength of our approach was to show that the distribution of %CV was different in subjects with type 1 diabetes and in those with type 2 diabetic on insulin treatment as indicated in figure 1. Reverting to the Rodbard's study [19] no difference was found in GV between type 1 and insulin-treated type 2 diabetes. However it should be noted that all patients were on basal-bolus insulin regimens while, in our study, approximately one half of the subjects with type 2 diabetes treated with insulin were on once-daily basal insulin alone. This difference in insulin regimens could explain the apparent discrepancies between the findings in the two studies. Even though the rationale for the selection of the upper limit of %CV in our reference group can be debated, this choice seems to be a posteriori validated by several observations. Firstly the upper limit of distribution in the reference group (36%), i.e. in type 2 diabetic patients treated only with diet and/or insulin sensitizers was approximately the same as that observed by using another approach that consisted to assess this upper limit after pooling in a single group all patients with type 2 diabetes without any hypoglycemia. Secondly, we observed a three to nine-fold increase in the frequency of hypoglycemia when adopting this threshold across the various groups of patients included in this study. In the group of persons with type 2 diabetes treated with DPP-4 inhibitors, no patient was above the threshold of 36%. In contrast, 12.3% of type 2 diabetes subjects treated with sulfonylureas were above this threshold of 36% and thus defined as unstable with a risk of hypoglycemia three times greater than in those below this threshold. Also, when utilizing this threshold of 36%, the percentage of insulin-treated patients designated as unstable was found to be as high as 19.0% and 55.7% in type 2 and type 1 diabetes, respectively. These observations were associated with the fact that in the present study the %CV progressively increased across the spectrum of diabetes from non-insulin-treated type 2 diabetes to insulin-treated type 2 diabetes and finally to type 1 diabetes. Our results are in agreement with those reported by Khonert et al [23] and by Midyett et al presented at the 76th meeting of the American Diabetes Association held on June 2016 [33]. In addition our findings indicate that GV is markedly increased in persons with diabetes irrespective of the group considered when compared to non-diabetic individuals [34]. These observations suggest that disease progression is reflected in worsening of GV compounded by the necessary escalation of treatment. However, it should be noted that there is no difference between patients with type 2 diabetes treated with basal insulin when compared with those on basal-bolus regimen.

Employing continuous glucose monitoring raises the question as to whether abnormally high glucose variability remains under diagnosed when using self monitoring of blood glucose,

especially in patients with type 2 diabetes treated with insulinotropic agents (sulfonylureas) and/or insulin therapy. Is there an argument in favor of a broader utilization of CGM data for detecting silent hypoglycemic events in such patients at least in those who are considered "vulnerable" and prone to hypoglycemia?

As frequency of hypoglycemic episodes might also result from lower mean glucose value [26,31,35,36] this parameter should be taken into account in interpreting our results. In the present study, the potential impact of a low mean glucose concentration on the incidence of hypoglycemia can be ignored in persons with type 1 diabetes, because the 24-h mean glucose values were similar in this group of patients, irrespective of the magnitude of the GV based on a %CV of >36% or ≤ 36%. Furthermore, the %CV has the main advantage of not being dependent on the mean glucose concentration [18,19].

The present work has a number of limitations. Firstly all measurements were made using an older generation of CGM but in our group of type 2 diabetic patients treated with insulin the means of %CV were approximately the same as the values observed at baseline in the population of the FLAT-SUGAR study [10,29] using a newer generation of CGM (DEXCOM SEVEN PLUS or G4). In addition all assessments of GV were limited to the monitoring of 24-h glycemic profiles on two consecutive days and the determination of a single parameter. In the future longer monitoring with newer generations of devices and other markers of GV may be required to confirm our findings. However, utilizing CGM is never devoid of between-and within-setting variations [37]. Finally the interstitial glucose value of 56 mg/dL (3.1 mmol/L), which was selected as threshold for hypoglycemia in the present study, is a compromise between the technical limitation of CGM and the definition of hypoglycemia that was set at 70 mg/dL by the ADA in 2005 [38]. With the older technology of CGM used in the present study, the monitoring system underestimated the real glucose value [7,39,40]. Throughout the time course of hypoglycemia, i.e. in non-steady state conditions, the relative difference between sensor readings and plasma glucose values varied between 0 and 20% [39]. In steady state conditions absolute differences of – 12 mg/dL [40] to – 19 mg/dL [7] were observed between interstitial glucose and the glucose value using the reference method when, like in the present study, the CGM was calibrated against capillary glucose concentrations. As it has been established that capillary and interstitial glucose values were underestimated at a similar extent when compared with the reference method [40], and as we have chosen to set the plasma-to-interstitial gradient at its upper limit of – 20%, a subcutaneous value of 56 mg/dL (3.1 mmol/L) corresponded approximately to a plasma glucose concentration of 70 mg/dL (3.9 mmol/L).

Despite these limitations, and in summary, it now seems timely to include targeting glucose variability to the assessment of chronic hyperglycemia utilizing HbA1c [11]. Our findings indicate that setting a threshold for GV based on %CV of blood glucose at 36% could be used to discern between stable and unstable glucose homeostasis. A more graded scale such as low, fair, moderate or high would also be welcome. The proposed threshold of 36% is supported by the observation of an increased frequency of hypoglycemia in patients with type 1 diabetes and in those with type 2 diabetes on insulin therapy as soon as this threshold is transgressed. Finally, we strongly recommend that more consideration be given to the assessment of GV, primarily in type 1 diabetes, but also in type 2 diabetes when on insulin treatment or more generally when any medication with a risk of hypoglycemia is implemented.

Duality of interest

All authors declare no competing interest with the content of the article

Author contributions

CC, AW, SD, ER and DO participated equally in the study design, data interpretation and critical revision of the manuscript. NM carried out the statistical analysis. LM participated in the study design, data collection and interpretation and writing of the manuscript. LM is also the guarantor of this work and as such had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Legends of figures

Figure 1: Histograms of relative frequency distributions for Coefficients of Variation for glucose (%CVs) in the 5 groups of persons with either type 2 (groups 1, 2a, 2b, and 3) or type 1 diabetes (group 4).

The upper limit of the distribution of %CV ($\%CV_{max1}$ = 36%) in group 1 (no insulinotropic agent) is taken as reference to discern stable from unstable diabetes. In the 4 other groups the percentages of patients above this threshold value of 36% are indicated as appropriate in the corresponding panels.

Figure 2: Incidence of hypoglycemia (upper panel) and results of 24-h mean interstitial glucose values given as medians with interquartile ranges, 10^{th} and 90^{th} percentiles (lower panel).

Statistical comparisons between groups 1, 2a, 2b, 3 and 4: (a) group 2b vs 1 and 2a ($p < 0.01$); (b) group 3 vs 1 and 2a ($p < 0.001$); (c) group 4 vs 1, 2a, 2b and 3 ($p < 0.0001$); (d) group 3 vs 1,2a and 2b ($p < 0.0001$); (e) group 4 vs 1 and 2a ($p < 0.0001$) and (f) group 4 vs 2b ($p< 0.01$).

Figure 3: Incidence of hypoglycemia (upper panel) and results of 24-h mean interstitial glucose values given as medians, with interquartile ranges, 10^{th} and 90^{th} percentiles (lower panel) when patients of each group were divided into 2 subgroups according to whether % CVs were > 36% or ≤ 36%.

Statistical significances are indicated when p values were < 0.05.

Table 1: Demographic, clinical and laboratory characteristics of the patients enrolled in the different groups

Groups of patients	Type 2 treated				Type 1	P
	Without any insulin secretagogue	With a DPP4 inhibitor + insulin sensitizers	With a sulfonylurea + insulin sensitizers	With insulin		
	(Group 1)	(Group 2a)	(Group 2b)	(Group 3)	(Group 4	
N°of subjects	N = 82	N = 28	N = 65	N = 79	N =122	
Age (years)	63 [56-67]	57 [55-65]	62 [57-69]	64 [59-73]	52 [43-72]	<0.0001
Men/women (n)	52/30	17/11	49/16	38/41	67/55	
BMI (kg/m^2)	30.2 [27.5-33.6]	29.9 [27.0-33.6]	28.7 [24.3-33.2]	29.6 [25.2-33.3]	24.2 [22.4-27.3]	<0.0001
Diabetes duration (years)	4 [2-8]	4.5 [1-8]	10.0 [4-17]	18 [11-28]	28 [20-35]	<0.0001
Diabetes treatment (%)						
Any insulin sensitizer	90.2	100	100	50.6	0	
Any DPP-4 inhibitors	0	100	0	0	0	
Any Sulfonylurea	0	0	100	53.2	0	
Type of insulin treatment if any - Basal regimen - Basal-bolus regimen - Pump therapy				41.8 58.2	0 79.5 20.5	<0.0001
HbA1c (%)	7.1 [6.8-7.7]	6.8 [6.4-7.0]	7.6 [7.1-8.6]	8.6 [8.0-9.2]	8.0 [7.4-8.9]	<0.0001
HbA1c (mmol/mol)	54 [51-61]	51 [46-53]	60 [54-70]	70 [64-77]	64 [57-74]	
24-h mean glucose concentration (mg/dL)	137 [123-151]	120 [113-131]	139 [125-165]	175 [153-207]	154 [136-198]	<0.0001
SD around the mean glucose value (mg/dL)	25 [19-33]	23 [19-28]	33 [24-43]	47 [36-61]	58 [44-73]	<0.0001
Percentage Coefficient of Variation for glucose (%CV)	18.1 [15.2-23.9]	18.6 [16.6-22.4]	23.7 [16.8-29.0]	27.8 [21.2-34.4]	37.2 [31.0-42.3]	<0.0001

All data are reported as medians and interquartile range [IQR]. Comparisons were made using non-parametric statistics and are indicated when significant ($p < 0.05$).